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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-------------------------------|-------------|----------------------|---------------------|------------------|
| 09/603,866 | 06/26/2000 | Avi J Ashkenazi | P1761R1 | 2405 |
| 7590 | 02/10/2005 | | EXAMINER | |
| Genentech Inc | | | KAUFMAN, CLAIRE M | |
| Attn: Diane L Marschang | | | ART UNIT | PAPER NUMBER |
| 1 DNA Way | | | | |
| South San Francisco, CA 94080 | | | 1646 | |

DATE MAILED: 02/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|------------------------------|------------------------|---------------------|--|
| | 09/603,866 | ASHKENAZI ET AL. | |
| | Examiner | Art Unit | |
| | Claire M Kaufman | 1646 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 22 November 2004.

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 2,4-11 and 50-54 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 2,4-11 and 50-54 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892)
2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____

4) Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .
5) Notice of Informal Patent Application (PTO-152)
6) Other: _____

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/12/04 has been entered.

The amendment filed 11/22/04 has been entered.

Response to Arguments

The rejection of claims 1, 5-11 and 49-54 under 35 USC 112, first paragraph, is withdrawn in view of the amendment to the claims.

Rejections of claims 1, 3 and 49 are moot in view of the cancellation of the claims.

Note the rejection of claims 11 and 54 as anticipated by Wiley et al. (Immunity 1995) under 35 USC 102 is withdrawn because the reference did not teach the lyophilized limitation. A new rejection appears below.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 102

Claims 2, 4-10 and 50-53 remain rejected under 35 U.S.C. 102(b) as being anticipated by Wiley (Immunity, 1995) for the reasons set forth in the previous Office action.

Applicants argue that the claims are not anticipated by Wiley because the buffer formulation of Wiley does not anticipate the claimed formulation and that the claimed formulation, as amended, must comprise zinc in an effective amount to stabilize the Apo-2L (TRAIL) trimer. The argument has been fully considered, but is not persuasive. It is maintained that the buffer of Wiley more likely than not had zinc in amounts sufficient to cause stable trimers of Apo-2L. The reasons are several fold. First, Wiley used Tris, and as stated in the previous Office action (middle of page 4): "Tris also appears to be what Applicants used (p. 48, line 13) to reconstitute the purified Apo-2L and what was the contributor of metals, including

zinc, shown in TABLE II.” Second, there is nothing to suggest that the Tris used by Wiley is different in composition or purity compared to the Tris used by Applicants. Both are apparently from a commercial source and would be assumed to be of sufficiently equivalent purity for the purpose used. Third, it was appreciated at the time the Wiley reference was published that TNF ligands and, most likely, TRAIL ligands were most active as stable trimers. In the Wiley reference beginning in the last sentence of page 676 through the end of the paragraph it is stated: “The crystal structures of TNF and LT α are known and these ligands have been shown to fold into β -pleated sheet sandwich structures and to form homotrimers.... These sequences in this region that are most conserved map to the stands that form these β -pleated sheets, with the centrally located D strand having the greatest conservation. Therefore, it is like that TRAIL, like TNF, forms an oligomeric structure that is necessary to cross-link its cognate receptor, thereby transducing a signal to the target cell.” On page 675, second to last sentence of first full paragraph, it also states, “Gel filtration analysis of the purified soluble TRAIL suggests that the native molecule is multimeric in solution....” In US Patent 5,763,223 (Wiley et al.), published before the effective filing date of the instant application, it is stated in col. 10, lines 61-65, “Certain members of the TNF family of proteins are believed to exist in trimeric form.... Thus, trimeric TRAIL may offer the advantage of enhanced biological activity.” Fourth, something which is old does not become patentable upon the discovery of a new property. The claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 195 USPQ 430, 433 (CCPA 1977). With regard to the above rejections, the PTO does not have facilities for examining and comparing Applicants' claimed ligand/buffer formulation with the prior art's, and thus Applicants have the burden of persuasion to make some comparison between materials in order to establish unexpected properties for the claimed invention. Applicants can be required to prove that prior art products do not necessarily or inherently possess characteristics of the claimed Apo-2L formulation. *Ex parte Gray*, 10 USPQ2d 1922 (BPAI 1989) and *In re Best*, 195 USPQ 430, 433 (CCPA 1977). Currently, it appears that the formulation of Wiley does inherently have all the characteristics of the claimed invention. It is maintained that Applicants' finding that biologically active trimers of Apo-2L are stabilized by zinc is an unappreciated property that was, nevertheless, inherently present in the prior art formulation.

New:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 2, 4-11 and 50-54 are rejected under 35 U.S.C. 102(b) as being anticipated by US 5,763,223.

US 5,763,223 teaches TRAIL (a.k.a. Apo-2L) with the sequence the same as that of SEQ ID NO:1 of the instant application, and purification of recombinantly produced active TRAIL in an aqueous buffer neutralized by the addition of Tris, pH 8 (col. 28, lines 66, through col. 29, line 2). Also taught is the TRAIL formulation in a lyophilized form (col. 19, lines 3-5). It is taught in col. 10, lines 61-65, “Certain members of the TNF family of proteins are believed to exist in trimeric form.... Thus, trimeric TRAIL may offer the advantage of enhanced biological activity.”

While US 5,763,223 is silent with respect to the presence and action of zinc in the formulation and its stabilization of a TRAIL trimer, it appears to be an inherent property of the formulation as supported by the following: Applicants formulated Apo-2L by addition of the purified Apo-2L to Tris, and state that “additional quantities of divalent metal ions were not added during fermentation or purification...” (p. 48, lines 11-13, of the specification). Applicants’ TABLE II (p. 48) shows that Tris was the apparent contributor of metals, including zinc. Applicants’ Apo-2L formulation appeared to comprised of what the TRAIL formulation of US 5,763,223 comprised. Therefore, the presence of zinc in an amount effective to stabilize TRAIL trimers is inherent to the formulation of US 5,763,223. Note that Applicants’ information is not necessary to support the rejection under 35 USC 102 by US 5,763,223, but is only presented as supporting evidentiary information.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (571) 272-0873. Dr. Kaufman can generally be reached Monday, Tuesday and Thursday from 8:30AM to 2:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (571) 272-0829.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Official papers filed by fax should be directed to (571) 273-8300. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. Please advise the examiner at the telephone number above before facsimile transmission.

Claire M. Kaufman, Ph.D.


Patent Examiner, Art Unit 1646

February 7, 2005